UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS' DAUBERT MOTION TO EXCLUDE CERTAIN LIABILITY OPINIONS OF PLAINTIFFS' EXPERT STEPHEN HECHT, PH.D.

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PRELIMINARY STATEMENT

Stephen S. Hecht, Ph.D. is an organic chemist and respected authority with regard to the creation and detection of nitrosamines, having begun his scientific research into this subject in the 1970s. Dr. Hecht's unchallenged qualifications in the field of organic chemistry support the reliability of his methodology. (Dr. Hecht 7/6/2021 R. 1-6 (Ex. 5 to Defs.' Mot.); Dr. Hecht CV (Ex. 1)).[1] Dr. Hecht holds a Ph.D. in organic chemistry from MIT, and held "a postdoctoral fellowship position at MIT in the laboratory of Professor Klaus Biemann, a pioneer in the application of mass spectrometry to organic chemical analysis."[2] Dr. Hecht has "carried out research related to nitrosamines continually since 1973," his research was "the first to characterize 'tobacco-specific nitrosamines' in tobacco products," and his "research paper in the 1978 Journal of the National Cancer Institute, describing these compounds, has been cited by the American Association for Cancer Research as a 'Landmark in Cancer Research.'" Dr. Hecht has worked in an academic and research setting since 1996. (Dr. Hecht 7/6/2021 R. 2-3). Dr. Hecht also "served as Editor-in-Chief of the American Chemical Society Journal *Chemical Research in Toxicology* from 2013-2017 and as an Associate Editor of the *Journal of Medicinal Chemistry* from 2004-2012." He has also "served on multiple writing groups for the International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans." (*Id.* at 3). Dr. Hecht's contributions to the peer-reviewed scientific literature are summarized in his report:

> I have published over 880 original manuscripts, book chapters, reviews, and other peer reviewed documents in the scientific literature. This includes more than 600 original research articles in peer-reviewed journals. More than half of these original research articles are concerned with nitrosamines, including

[1] Unless otherwise noted, all exhibits are attached to Adam M. Slater's certification in opposition to Defendants' motion.

[2] Mass spectrometry is the method used to identify the NDMA and NDEA in the contaminated valsartan.

> nitrosodimethylamine (NDMA), also known as dimethylnitrosamine (DMN). My H index is 91, and my articles have been cited more than 35,000 times.
>
> My first publication on nitrosamines was in 1974 when my colleagues and I discovered N'-nitrosonornicotine (NNN) in smokeless tobacco. This was the first example of a carcinogenic nitrosamine in unburned tobacco; in fact, the first example of any carcinogen in unburned tobacco. This paper was published in Science, and revolutionized the characterization and carcinogenicity assessment of tobacco products.

(*Id.* at 4). Dr. Hecht's scientific work and qualifications continue to be relevant today:

> Thus, as a result of more than 45 years of research in chemical and tobacco carcinogenesis, much of it focused on nitrosamines, I am thoroughly familiar with the state of the art in the formation, quantitative analysis, chemistry, biochemistry, metabolism, carcinogenicity, human exposure biomarkers, and DNA damage by nitrosamines. I currently serve on the European Food Safety Authority panel evaluating nitrosamines in food. **I also served on the expert panel for the FDA Workshop entitled "Nitrosamines as Impurities in Drugs: Health Risk Assessment and Mitigation Public Workshop," March 29, 2021**.

(*Id.* at 6; Dr. Hecht 8/17/2021 Dep. Tr. 155:16-24 (Ex. 2)).

Dr. Hecht's qualifications and knowledge base to opine on this subject cannot be reasonably disputed, and his methodology is rooted in scientific research and the peer-reviewed literature, which are the touchstones of methodological validity. Defendants ignore this and resort to mischaracterizations of Dr. Hecht's opinions and the underlying facts, partial citations, and hyper-technical but inconsequential attacks on Dr. Hecht's methodology.[3]

[3] Defendants note in passing that Dr. Hecht did not offer liability opinions specific to Teva or Torrent. Defendants are certainly aware of (though they avoided asking him any questions about) Dr. Hecht's October 31, 2022 report, which states in part: "The available knowledge and technology should have been applied to add straightforward testing for NDMA and NDEA of **each batch of API and finished dose manufactured using the API manufactured with these processes**, which would have revealed the presence of the NDMA and NDEA." (Dr. Hecht 10/31/22 R. 11). The extent to which his opinions about what was known in the scientific community, and when, may be deemed relevant to those defendants, and may be deemed

In essence, the defense previews a cross-examination that would go to the weight of the conclusions reached, at most, but in no way would establish that Dr. Hecht failed to apply an acceptable scientific methodology. The motion should be denied.

STATEMENT OF FACTS

The NDMA and NDEA that contaminated ZHP's valsartan API were formed as a direct result of the two ZHP-created manufacturing processes at issue—the TEA with sodium nitrite quenching process and the zinc chloride process. The root cause of the formation of these genotoxic, carcinogenic impurities is described in multiple ZHP internal documents,[4] for example the email written by ZHP employee Jinsheng Lin, Ph.D. on July 27, 2017, to multiple high-level employees of ZHP. Dr. Lin, whose job was to identify impurities in ZHP drug products and their mechanism of creation, confirmed that there was NDMA in ZHP's valsartan, that this was caused by the quenching of sodium azide with sodium nitrite, that this was a known problem with the manufacture of sartans, and that this was a serious cGMP problem. (Jinsheng Lin, Ph.D. July 27, 2017 email, English translation, ZHP00190573 (Ex. 7); Min Li 4/20/21 Dep. Tr. 82:11-83:7, 85:7-86:2, 86:6-14, 87:19-88:7, 88:13-90:2, 90:7-10, 90:14-23 (Ex. 8)). Later, after the impurities were discovered by ZHP API customer Novartis (in Ireland), forcing ZHP to finally disclose this serious problem, ZHP concluded in its Deviation Investigation Reports that the root cause for the creation of the NDMA/NDEA was the sodium nitrite quenching of sodium azide—matching what Dr. Lin

admissible, will depend on the context at trial. This is not an issue to be determined at this juncture.

[4] The FDA has concluded that "NDMA and NDEA are probable human carcinogens and should not be present in drug products," the EPA considers NDMA and NDEA to be probable human carcinogens, and **USP has said, "their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens**." (FDA, *FDA presents interim limits of nitrosamines in currently marketed ARBs* (Dec. 19, 2018) (emphasis added) (Ex. 3); EPA, *N-Nitrosodimethylamine* (Ex. 4); EPA, *N-Nitrosodiethylamine* (Ex. 5); USP, Summary, Highlights and Timeline of General Chapter <1469> Nitrosamine Impurities (July 20, 2018) (Ex. 6)).

said in his email a year earlier. (PRINSTON00075810-11, 75854 (Ex. 9)). Aside from the very troubling implications of this email, it completely belies ZHP's primary (false) narrative, that nobody knew or could have known about the risk of nitrosamine formation before June 2018.

ZHP's fanciful narrative that nobody could have understood the risk of the potential presence of the amines and these well-known chemical reactions relies largely on out of context overreading of general FDA statements about the nitrosamine contamination. In fact, Defendants fail to acknowledge that one of the FDA statements makes a point of emphasizing the failings by ZHP that caused the contamination:

> We've placed a ZHP facility on import alert to stop all its API and finished drugs made using ZHP's API from legally entering the U.S. We also issued them a warning letter outlining several manufacturing violations, including impurity control, change control and cross contamination from one manufacturing process line to another. It's unlikely that the subtle problems causing these impurities could have been found on a routine current good manufacturing practice (CGMP) inspection. Nonetheless, our inspections did reveal systemic problems of supervision that could have created the conditions for quality issues to arise.

FDA Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues, p. 2 (Jan. 25, 2019) (Ex. 10).[5]

The FDA directly addressed the cGMP violations, the resulting adulteration of the valsartan, and emphatically rejected ZHP's excuse for its failings, in more detail in the November 30, 2018 Warning Letter issued to ZHP:

> **This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).**

[5] The "routine current good manufacturing practice (CGMP) inspection" referenced is the routine inspection performed by the FDA. Thus, the FDA made clear that it was not in a position to discover the nitrosamine contamination based on the information made available by ZHP to the FDA during routine inspections—while the FDA clearly found that the fault was with ZHP.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, **your API are adulterated** within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

* * *

In November 2011 you approved a valsartan API process change (PCRC - 11025) that included the use of the solvent DMF. Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. **Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine.** According to your ongoing investigation, dimethylamine is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility.

You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change. You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.

Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that your process development study was adequate. **We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce.**

(PRINSTON00077339, 342 (emphasis added) (Ex. 11)).

[redacted]

(ZHP00662308 (Ex. 12)). This language was removed from the final draft, but the truth remains. ZHP has formally stipulated that it did not consult any scientific literature regarding potential risks of utilizing sodium nitrite along with DMF and its potential impurity/degradation product dimethylamine ("DMA") in the zinc chloride manufacturing process. (Ex. 13). [redacted] (Min Li 4/21/21 Dep. Tr. 408:13-24, 409:16-410:21 (Ex. 14)).

Dr. Hecht has explained that the use of sodium nitrite to quench the sodium azide, which was introduced in the two offending manufacturing processes, should have been fully assessed from the outset. His reports provide great detail, and his deposition testimony summarizes the issue; "[W]here they're adding sodium nitrite at pH[redacted], they should have tested for nitrosamines." (Dr. Hecht 1/13/23 Dep. Tr., 118:3-119:9). Again, this is what Dr. Lin was saying in his July 2017 email.

Dr. Hecht explained his methodology during his deposition, and in particular the underpinning for his opinion that "any organic chemist involved in the development or assessment" of the offending processes should have realized the potential for nitrosamines to form:

> A. I looked in the literature to see whether, you know, the contamination of DMF with dimethylamine or the formation of dimethylamine from DMF was, you know -- was reported. I mean, there's no doubt that DMF can hydrolyze to dimethylamine when you heat it for [redacted] hours at [redacted] degrees, or whatever it was. I mean, that's like basic organic chemist -- chemistry. Yeah, I mean, I think, quote, any organic chemist would know that.
>
> But there's also a fair amount of literature on just contamination of DMF with dimethylamine. I think I noted before that sometimes it has a fishy odor, due to the dimethylamine. But there's -- you know, there's published literature. I mean, you know, I have a paragraph here from Fields, you know, "methods for removing the FMOC group."
>
> (Court Reporter Clarification.)

A. FMOC, F-M-O-C. In Methods in Molecular Biology, Volume XXXV, Peptide Synthesis Protocols, published in 1994 by Humana Press in Totowa, New Jersey.

And what that -- within that volume -- within that volume on page 22, it says that "amine impurities that could possibly remove the FMOC group include dimethylamine found in DMF," and then it references Number 47. I'm not sure what 47 was.

But anyhow, you know, this is like -- this is not something new. I mean, DMF has been around a long time, and this is -- this is not new, that there might be some dimethylamine in the DMF, or the dimethylamine could form when you heat DMF at [redacted] degrees for [redacted] hours.

* * *

A. The answer is awareness. Okay? If you're developing a specific process, it's your responsibility to be aware of all aspects of that process. Not only just that, "Oh, this process works, because it gives us a high yield and it's less expensive, so this is going to give us a great yield of our product." No.

You have to know all possible aspects. You have to consider the possible hazards that are involved with your -- with your process, and you have to consider the possible costs that are involved with your process. You have to consider the environmental impact of the process that you're using. You have to consider whether the drug that you're making, if you're making a drug, is going to have toxicity. **It all has to do with the awareness of the particular part of organic chemistry that you're working in. You can't be -- you can't know everything, but you have to be aware of the specific aspects of the process, and its possible consequences, that relate to this particular reaction conditions that you're using. It's awareness**.

* * *

A. You can't be -- it's impossible to be aware of everything. But you do -- it is your responsibility to be aware of the aspects that relate to your particular process. That is absolutely basic.

(Dr. Hecht 1/13/23 Dep. Tr., 94:6-95:12, 98:15-99:11, 99:19-23 (Ex. 1 to Defs.' Mot.)). Dr. Hecht explained the "wide knowledge" of nitrosamine formation in existence since at least 1970,

including by those working in pharmaceutical development, and needed to be taken into account by the Defendants, but was not:

> A. Yes, generally. But pharmaceuticals is one aspect of it, okay? And people -- investigators, chemists from drug companies, pharmaceutical companies, attended the meetings that discussed nitrosamine formation. Okay? They attend the American Chemical Society meeting, where nitrosamine formation, nitrosamine formation, nitrosamine carcinogenicity, nitrosamine chemistry is discussed. So they are aware.
>
> * * *
>
> A. No, not specifically for this process, okay? I'm saying the general mechanism of formation, okay? So that is the beauty of chemistry, okay? You have certain reactions that will take place under certain conditions, and it doesn't matter whether that's in a food product or a pharmaceutical product, or in the environment. Okay? We can predict that that reaction will take place.
>
> And the formation of dimethylnitrosamine from dimethylamine has been known for decades.

(Dr. Hecht 1/13/23 Dep. Tr., 128:7-15, 129:7-16).

As a result of the failure to account for the potential risks of the chemicals and reactions introduced by ZHP's changes to the manufacturing process, ZHP failed to test for the presence of nitrosamines. The technology to do so, either GC-MS (gas chromatography-mass spectrometry) or LS-MS (liquid chromatography-mass spectrometry), was readily available beginning long before the development and use of these processes, as admitted by ZHP's expert on that point, Dr, Xue. (Xue Dep. Tr. 247:20-248:11 (Ex. 15)). This was documented in the literature, for example the 1978 IARC publication *Some N-Nitroso Compounds*, which states, "The principal techniques employed for the analysis of volatile *N*-nitros-amines have been described in a recent publication (Presussman, *et al.*, 1978)," and "[t]he relative merits of high- and low-resolution mass spectrometry are discussed, since use of mass spectrometry as a confirmatory technique is

particularly important." (P. 40 (Ex. 16)). Another article, published in 2008, titled *Identification and Control of Impurities for Drug Substance Development using LC/MS and GC/MS*, discusses the use of GC-MS and LC-MS to identify impurities in the pharmaceutical industry. (Ex. 17). In fact, ZHP's own documents demonstrate the use by ZHP of GC-MS to evaluate ZHP manufactured drug substances, going back to at least 2009. (ZHP01746278 (Ex. 18); SYNCORES00001458 (Ex. 19); SOLCO00027588 (Ex. 20)). This technology was readily available and should have been used during the development process, and thereafter once manufacturing began for commercial sale, and this would have identified the NDMA and NDEA without difficulty.

We know that the presence of NDMA and NDEA would not have been difficult to identify, because ZHP customer Novartis did exactly that in June 2018. (ZHP00359798 (Ex. 21)). And as set forth above, ZHP knew this at least as of July 2017 but told nobody. Novartis had noted small unknown peaks on standard gas chromatography, and when ZHP failed to identify the source of those peaks, Novartis did so on its own. [redacted] (ZHP01390018 (Ex. 22)). Novartis thus identified the NDMA and [redacted] with one hand tied behind its back, since Novartis did not know the full process and all substances and chemicals used in the manufacturing process. On the other hand, ZHP obviously did have this information along with the entire route of synthesis ("ROS").

[redacted]

(Peng Dong 3/31/21 Dep. Tr. 277:2-306:19 (emphasis added) (Ex. 23)). [redacted] (Peng Dong

4/1/2021 Dep. Tr. 446:2-465:9 (Ex. 42); Peng Dong 4/2/2021 Dep. Tr.480:10-481:12 (Ex. 43)).

[redacted] (Min Li 4/21/21 Dep. Tr., 381:1-390:20, 467:14-470:7). In turn, Dr. Hecht has applied his expertise and confirmed "the inadequate scientific risk assessment performed by ZHP" and that "[s]cientifically reasonable process research, study, and understanding of potential nitrosamine impurities, would have resulted in recognition of the risk of creating the nitrosamine impurities, and testing that would have demonstrated the presence of these impurities." (Dr. Hecht 10/31/22 R. 4 (Ex. 6 to Defs.' Mot.)). As further confirmed in his deposition, the potential for and occurrence of the NDMA and NDEA contamination would have been identified by ZHP with "a sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products" and with "science-based decision-making with respect to the potential risks of those processes." (Dr. Hecht 1/13/23 Dep. Tr. 294:10-296:8).

Dr. Hecht's methodology, incorporating his knowledge, experience, and analytical capabilities, along with scientific literature, ZHP's own confirmatory findings in its deviation investigation, and ZHP's internal documents and corporate testimony, cannot be reasonably challenged.

LEGAL ARGUMENT

I.

DR. HECHT IS QUALIFIED TO OFFER HIS OPINIONS

Defendants do not challenge Dr. Hecht's qualifications to offer his opinions in the field of organic chemistry. Defendants do argue that Dr. Hecht cannot offer regulatory opinions, but limit their motion as to Dr. Hecht to the following narrow caveat: "Drs. Najafi and Hecht are not qualified to offer opinions on whether defendants' manufacturing practices or processes adhered to state and federal regulations, because neither possesses any regulatory experience." (Def.' Br. 22-23).

Accordingly, Dr. Hecht will not offer the regulatory opinion at trial as to whether defendants' manufacturing practices or processes adhered to state and federal regulations. To be clear, Dr. Hecht's opinions will be phrased in terms of organic chemistry and science, and whether, for example, the risk assessment performed by ZHP constituted "a sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products." (Dr. Hecht 1/13/23 Dep. Tr. 294:10-296:8). That testimony can then be considered and relied on in determining whether the governing standards requiring "a sound scientific appraisal" were met.

II.

DR. HECHT'S METHODOLOGY IS RELIABLE

Dr. Hecht's extensive experience and expertise with regard to nitrosamines, and application of that experience along with peer reviewed and academic literature, establishes the reliability of his methodology. Though couched as criticism of the reliability of the opinions, Defendants are

actually arguing with Dr. Hecht's knowledge, his interpretation of methodologically valid sources of relevant scientific information, and the conclusions he reached, which is not an appropriate *Daubert* challenge.

The focus of the reliability inquiry is on the expert's principles and methodology, not on his or her conclusions. *Glynn v. Merck Sharp & Dohme Corp.*, Nos. 11–5304, 08–08, 2013 WL 1558690, at *2 (D.N.J. April 10, 2013) (citing *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594-95 (1993)) (Ex. 24). The basis for this Court's finding that an expert should be precluded under *Daubert* in another case demonstrates by comparison why Dr. Hecht's opinions are appropriate here. *Player v. Motiva Enterprises LLC*, No. Civ. 02–3216(RBK), 2006 WL 166452, at *6-7 (D.N.J. Jan. 20, 2006) (citations omitted) (Ex. 25). In *Player*, this Court found an expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, among other things, and held: "His method is untestable and arbitrary, without a generally accepted, established, or peer-reviewed methodology, and his evaluation was conducted without any real standards." *Id.* at *7-8. None of those criticisms apply to Dr. Hecht's methodology. *Geiss v. Target Corp.*, No. 09–2208 (RBK/KMW), 2013 WL 4675377, at *4 (D.N.J. 2013) (Ex. 26) (quoting *Elcock v. Kmart Corp.*, 233 F.3d 734, 745-47 (3d Cir. 2000)). This is especially true since, "Rule 702 has a liberal policy of admissibility." *Geiss*, 2013 WL 4675377 at *4 (citing *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir. 2008) (other citations omitted)). "A court should not, however, usurp the role of the fact-finder; instead, an expert should only be excluded if the flaw is large enough that the expert lacks the 'good grounds' for his or her conclusions." *In re Zoloft Prods. Liab. Litig.*, 858 F.3d 787, 792-93 (3d Cir. 2017).

Defendants' primary focus is on Dr. Hecht's opinion that the chemists involved in the development and assessment of the two manufacturing processes at issue should have accounted

for the potential creation of nitrosamines. Defendants argue that the opinion is improper since there was not an article identified that mimicked the exact process and conditions used with the two manufacturing processes. There is of course no requirement that an article have been published analyzing the risks of the actual processes at issue, or mirroring the exact same conditions, for the expert to rely on it. The expert can interpret, understand, and apply scientific literature and explain the scope of what is indicated, from the expert's highly informed perspective. *See Westley v. Ecolab, Inc.*, No. Civ.A.03–CV–1372, 2004 WL 1068805, at *6 (E.D. Pa. 2004) (Ex. 37) (holding: "[the chemist's] opinion is primarily based on his experience and knowledge of chemicals and specifically his knowledge of aluminum hydroxide and potassium hydroxide and their potential effects on human tissue, as well as the facts related by Plaintiff. **Opinions based solely on experience and knowledge are sufficient under *Daubert*.**" (emphasis added) (citing *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 809 (3d Cir. 1997) ("holding expert testimony admissible where expert 'relied on general experience and readings, general medical knowledge, standard textbooks, and standard references'")). As the Supreme Court explained in *Kumho Tire*, the objective of *Daubert* "is to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). Indeed, the *Daubert* test "may be more flexibly applied in cases where the expert testimony is based on experience." *In re Front Loading Washing Mach. Class Action Litig.*, Civil Action No. 08–51(FSH), 2013 WL 3466821, at *2 (D.N.J. July 10, 2013) (Ex. 44).

The key point is that it was foreseeable that dimethylamine could be introduced to the zinc chloride process via the DMF. As stated in Dr. Hecht's reports, one avenue for this to occur was

as an impurity of the DMF as commercially sold, and another was for the dimethylamine to form during the process:

> The documents from ZHP clearly demonstrate how the formation of NDMA could have been avoided. They identified three critical factors: 1) use of dimethylformamide in the tetrazole formation step, and **the dimethylformamide may have contained trace amounts of dimethylamine or the dimethylamine was formed during the process**; 2) quenching of azide using nitrous acid (formed from nitrite under acidic conditions); and 3) quenching takes place in the presence of the product. ZHP concluded that NDMA was formed only when all 3 factors were present, based on extensive analysis by ZHP. Factor 2 should have raised a *RED FLAG* for the potential formation of nitrosamines. **The contamination of dimethylformamide with dimethylamine or the formation of dimethylamine during the process was foreseeable, and should have been evaluated.**

(Dr. Hecht 7/6/21 R. 20 (bold emphasis added)).[6] In addition to the deviation investigation reports, Dr. Hecht also noted in his reports that ZHP and its witnesses have admitted to both pathways, including in the August 26, 2018 letter to the FDA, signed by Jun Du. (Dr. Hecht 10/31/22 Report, at 2-3 (citing Min Li 4/20/21 Dep. Tr., 77:8-80:16 (Ex. 8); Jun Du 5/28/21 Dep. Tr., 232:18-234:6 (Ex. 27)).[7]

Dr. Hecht relied on his extensive knowledge and experience, and examples of scientific literature addressing the potential for the amines to exist as contaminating impurities of the

[6] Dr. Hecht documented the same opinion with regard to the TEA with sodium nitrite quenching process, and confirmed that the analysis of the inadequate assessment found by the FDA in its Warning Letter also described the issues with the TEA with sodium nitrite quenching process. (Dr. Hecht 7/6/21 R.21; Dr. Hecht 1/13/23 Dep. Tr., 296:21-300:12).

[7] Defendants' argument that Dr. Hecht first addressed this issue in his deposition is belied by his reports, which clearly present the issue. Even if defendants were correct that they were hearing something for the first time at the deposition, they had the opportunity to depose the expert on those matters and thus are not prejudiced. *nCube Corp. v. SeaChange Int'l, Inc.*, 809 F. Supp. 2d 337, 347 (D. Del. 2011) (noting that "whether the objecting party had notice of the subject matter of the testimony based on the contents of the report and elaborations made during any deposition testimony").

solvents prior to introduction to the processes. This includes the following: "DMF sold commercially contains trace amounts of methanol, water, formic acid, and dimethylamine." (Long, G., Meek, M.E. *Concise International Chemical Assessment Document 31: N,N-Dimethylformamide.* at 5 (WHO 2001) (Ex. 28)) (Dr. Hecht Supplemental Reliance List, item 14 (Ex. 29)). "Formic acid and dimethylamine are thus predominant impurities in DMF and determine the odor of the impure solvent." (Juillard, J. *Dimethylformamide: Purification, Tests For Purity And Physical Properties.* Int'l Union of Pure and Applied Chem. Pergamon Press pp. 885-892, at 887 (1977) (Ex. 30)) (Dr. Hecht Supplemental Reliance List, item 15). Yet another in the context of introduction of diethylamine through the TEA used in the TEA process (Defendants incorrectly assert no such literature has been identified), in discussing use of commercially available samples of triethylamine: "Triethylamine was also checked for removal of any diethylamine by using the procedure of Schweinsberg and Sander." (Gowenlock, B.G., Hutchinson, R.J., Little, J., Pfab, J. *Nitrosative dealkylation of some symmetrical tertiary amines.* J. Chem. Soc., Perkin Trans. 2, at 1110 (1979) (Ex. 31)) (Dr. Hecht Supplemental Reliance List, item 3).[8] Dr. Hecht made the point that this was well-known when questioned during his deposition as well: "In fact, DMF sometimes has a fishy odor due to the dimethylamine. So, you know, dimethylamine is a potential contaminant of DMF, that's well-established." (Dr. Hecht 1/13/23 Dep. Tr., 52:24-53:5, 93:19-95:12).

During its deviation investigation, ZHP went back and reviewed the supplier information for the DMF utilized in the zinc chloride process, which indicated how the DMF was made and the risk that dimethylamine would be a resulting contaminant: [redacted]

[8] [redacted] (PRINSTON00075927 (Ex. 9)).

[redacted] (PRINSTON0075961 (Ex. 9)). Thus, ZHP's own investigation has confirmed it was on notice of—but ignored—the potential presence of DMA in the DMF through the information provided by the supplier. In addition, Certificates of Analysis obtained by Plaintiffs for DMF and TEA sold by the same manufacturers who sold the DMF and TEA used by ZHP demonstrate that dimethylamine was listed as an impurity of the DMF (Shandong Hualu-Hengsheng Chemical Co., Ltd., COA, Batch No. 20101026 (Ex. 32) and diethylamine was listed as an impurity of the TEA (Zhejiang Jianye Chemical Co., Ltd, COA, 11/25/12 (Ex. 33)).[9]

Defendants also attempt to refute the applicability of the literature addressed to the potential for the amines to form during the manufacturing processes, focusing exclusively on literature indicating that DMF "decomposes slightly at its normal boiling point to give small amounts of dimethylamine" as if that is a complete statement of the only conditions under which dimethylamine can form. Amarego and Perrin, Purification of Laboratory Chemicals, Fourth Edition, at 192 (1996) (Ex. 13 to Defs.' Mot.); J. Muzart, *N,N-Dimentylformamide: much more than a solvent*, Tetrahedron 65, 8313-23 (2009) (Ex. 14 to Defs.' Mot.) (same). Moreover, this argument is presented as if ZHP identified this literature and determined it was inapplicable based on the reference to the boiling point during the development and use of the process, and

9 [redacted] (PRINSTON0075953-59, Ex. 9).

accordingly there was no issue to investigate. But this never happened since they failed to consult any literature. Thus, Defendants are essentially arguing from a place of gross, biased speculation that if that literature had been noted, it would have been found to be irrelevant—and that ignoring the risk would have been appropriate, which is absolutely wrong. [redacted] (Eric Gu 4/5/21 Dep. Tr., 172:13-174:9, 183:12-21 (Ex. 34)). Dr. Hecht opines to the importance of this literature based on what the chemists at ZHP should have understood and that is absolutely appropriate.

In addition, Defendants studiously ignore the fact that the literature is far broader, and the pathways are not limited to degradation at the boiling point. This includes, "Owing to its various modes of degradation (hydrolysis, thermal and photochemical decomposition) the principal impurities found in DMF are: dimethylamine…" (Juillard, *supra*, at 890 (Ex. 30)) (Dr. Hecht Supplemental Reliance List, item 15). This means that the DMF can degrade and yield dimethylamine due to multiple independent factors: exposure to water, due to the impact of temperature—without specifying the need to reach the boiling point—and due to light; in fact, dimethylamine is an intrinsic DMF impurity, in part, because DMF degrades to form dimethylamine in so many ways. Similarly, "In its anhydrous state, DMF is a relatively neutral solvent with a pH of 6.3, which, upon exposure to water, undergoes hydrolysis to produce formic acid (FAH) and dimethylamine (DMA)." (Noel et al., *Unveiling the Influence of pH on the Crystallization of Hybrid Perovskites, Delivering Low Voltage Loss Photovoltaics*, Joule 1, at 329 (Oct. 11, 2017) (citing 1992, 2003, 2011 publications at references 30-32) (Ex. 35) (Dr. Hecht Supplemental Reliance List, item 4)). And another states, "It has long been known that DMF is not stable over a long period of time, and, in the presence of water, degrades to the secondary

amine, dimethylamine (DMA) and formic acid (FA)…." (Magtaan, et al., *Regeneration of aged DMF for use in solid-phase peptide synthesis*, J. Pep Sci., at 1 (2019) (citing 1988, 1994 publications at references 17-18) (Ex. 36)) (Dr. Hecht Supplemental Reliance List, item 4)). These illustrative examples are more than sufficient from a methodological perspective, and make clear that the two articles citing the boiling point are only a part of the cumulative whole that was ignored.

Defendants make a similar argument in the context of the TEA with sodium nitrite quenching process; however, the risk of nitrosation due to the introduction of TEA and tertiary amines in general, followed by sodium nitrite, was also foreseeable based on the scientific literature. *See* Smith, P.A.S. & Loeppky, R.N. *Nitrosative Cleavage of Tertiary Amines, J. of the Am. Chem. Soc.* 89 (5), 1147-1157 (1967) ("In actual fact, Guether reported correctly in 1864 that triethylamine is converted to diethylnitrosamine by aqueous nitrous acid.") (Footnote 31 to Dr. Hecht's 7/6/2021 R.) (Ex. 38); Fiddler, W., Pensabene, J., Doerr, R. et al. *Formation of N-Nitrosodimethylamine from Naturally Occurring Quaternary Ammonium Compounds and Tertiary Amines.* Nature 236, 307 (1972) ("The nitrosative cleavage of tertiary amines is not new and has been described before.") (Ex. 39) (Dr. Hecht Supplemental Reliance List, item 11); Sun, Z., Liu, Y.D., and Zhong, R.G. *Theoretical investigation of N-nitrosodimethylamine formation from nitrosation of trimethylamine.* J. Phys. Chem. A. 114, 455-65 (2010) (ZHP 211) (Tertiary amines have been demonstrated to be capable of undergoing nitrosative cleavage to produce carcinogenic N-nitrosamines.") (Ex. 40); PRINSTON0076108 (citing Sun, supra, and stating, [redacted]) (Ex. 41)).

As discussed above, it is the role of the expert to interpret and explain the significance of

the literature, which is what Dr. Hecht has done. He explained in his deposition that the literature is illustrative of the information the chemists at ZHP should have reviewed and known, and explained that the existing literature was more than sufficient to place those chemists on notice of the risk of nitrosation in both processes, and the need to test for NDMA and NDEA.[10] In responding to questioning on the significance of the reference to the boiling point of DMF in some of the articles, he made clear that dimethylamine could be produced under the conditions used in the zinc chloride process since the heating was to a temperature near to the boiling point for approximately [redacted] hours, in an aqueous solution: "I mean, there's no doubt that DMF can hydrolyze to dimethylamine when you heat it for [redacted] hours at [redacted] degrees, or whatever it was…." (Dr. Hecht 1/13/23 Dep. Tr., 94:6-95:12). Dr. Hecht explained the proper approach to questions in organic chemistry: "I'm saying the general mechanism of formation, okay? So that is the beauty of chemistry, okay? You have certain reactions that will take place under certain conditions, and it doesn't matter whether that's in a food product or a pharmaceutical product, or in the environment. Okay? We can predict that that reaction will take place." (*Id.* at 129:8-16). As one Court stated in rejecting a *Daubert* challenge and recognizing that the role of the expert includes interpretation of relevant technical or scientific information: "Expert testimony will help the jury comprehend those documents and will highlight the important aspects of the data…." *Wolfe v. McNeil-PPC, Inc.*, 881 F.Supp.2d 650, 660 (E.D. Pa. 2012). That is exactly what Dr. Hecht has done, and will do at trial. The point is that the literature, taken collectively, should have been identified and considered by ZHP, and it was not. The suggestion by Defendants that Dr. Hecht's opinions on

[10] Defendants pick out a few statements where Dr. Hecht responds to questions asking whether scientific information was "widely known"; however, Dr. Hecht was very clear that he was focused on what the chemists responsible for developing and assessing the processes should have been aware of. (Dr. Hecht 1/13/23 Dep. Tr., 79:6-11).

this issue are no more than unreliable ipse dixit is obviously wrong.

And ZHP performed testing that proved Dr. Hecht is correct! [redacted] (PRINSTON00075811 (Ex. 9)). [redacted] (PRINSTON00075927 (Ex. 9)). Thus, Dr. Hecht is not just relying on his vast knowledge and experience in the field of organic chemistry, and the scientific literature, but also has ZHP's own confirmatory testing. In the face of this, it is hard to understand how ZHP can characterize Dr. Hecht's opinion as an "untested assumption." (Defs.' Br. 12-13).

Defendants fail to mount a consequential attack on Dr. Hecht's methodology. They can cross-examine and attempt to present countering testimony at trial, but the opinions are all proper and admissible.

CONCLUSION

For the foregoing reasons, Defendants' motion to preclude certain of Dr. Hecht's opinions should be denied.

Respectfully,

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CERTIFICATE OF SERVICE

I hereby certify that on April 11, 2023, I electronically filed a partially redacted version of this brief and my supporting certification with the Clerk of the Court using CM/ECF system which will send notification of such filing to the CM/ECF participants registered to receive service in this MDL. In addition, I hereby certify that unredacted copies of foregoing document will be served contemporaneous to filing via email on the Court, Special Master, and the Defense Executive Committee at DECValsartan@btlaw.com, with the exception of the unredacted exhibits, which will be sent to the Court on a thumb drive via FedEx and to the Defense Executive Committee via a Dropbox link.

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Dated: April 11, 2023